**REMARKS**

Claims 49-57 were pending in this Application.

Applicant acknowledges that Claims 53-54 have been allowed by the Examiner.

By this Amendment, Applicants canceled Claim 52 and submits previously presented Claims 49-51 and 55-57 for consideration by the Examiner.

By this Amendment, Applicants proposed new Claims 58-62 which are directed to the synergistic combination of prenyl-protein transferase inhibitor with an antineoplastic agent selected from parlitaxel, epothilone A, epothilone B, desoxyepothilone A or desoxyepothilone B. The Examiner to whom this Application has been assigned stated that "claims directed to the synergistic combination of prenyl-protein transferase inhibitor with an antineoplastic agent selected from parlitaxel, epothilone A, epothilone B, desoxyepothilone A or desoxyepothilone B will be examined."

By this Amendment, Applicants also proposed new claims 63-69 which are directed to the synergistic combination of prenyl-protein transferase inhibitor with an antineoplastic agent selected from epothilone and taxol, which are different classes of microtubule-stabilizing compounds. Applicant maintains that proposed new Claims 63-69 are well supported by the specification as originally filed. The specification as filed clearly states the advantage and method of administering a combination of an antineoplastic agent and a prenyl-protein inhibitor to affect prenylation of protein, DNA replication, apoptosis and/or the stability of microtubules at the same time to achieve a therapeutic anti-cancer effect.

Accordingly, there is no issue of new matters and Applicants respectfully request the entry of this Amendment. Upon entry of this Amendment, Claims 49-51 and Claims 53-69 will be pending and under examination.

**37 CFR §1.75 Rejection**

The Examiner rejected Claim 52 under 37 CFR §1.75 "as being substantially duplicate of Claim 53. The Examiner stated that "when two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantially duplicate of the allowed claim."

In response but without conceding the correctness of the Examiner's position and to expedite the prosecution of this Application, Applicants have canceled Claim 52 without prejudice. New Claims 58-69 do not contain the above mentioned issues, thereby rendering this ground of rejection moot.

**35 U.S.C. §112, First Paragraph Rejection**

The Examiner rejected Claims 49-51 and 55-57 under 35 U.S.C. §112, first paragraph. The Examiner suggested that the specification "does not reasonably provide enablement for the term 'an antineoplastic agent which is a microtubule-stabilizing agent.'" The Examiner stated that "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." The Examiner also stated that the "terms 'an antineoplastic agent which is a microtubule-stabilizing agent' in Claims 49-51 and 55-57 lack clear exemplary support in the specification as filed."

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Manual of Patent Examining Procedure (MPEP) §2164.01(a) sets forth the factors the Examiner must consider in determining "whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement [of 35 U.S.C. §112, first paragraph,] and whether any necessary experimentation is undue." These factors include, but are not limited to: 1) nature of invention, (2) state of prior art, (3) level of ordinary skill in the art, (4) level of predictability in the art, (5) amount of direction and guidance provided by the inventor, (6) existence of working examples, and (7) breadth of claims, and (8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The Examiner alleged that the above-mentioned factors were considered in making the rejection under 35 U.S.C. §112, and the Examiner cited In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1998) for his support. In In re Wands, the court reversed the USPTO's determination that claims directed to methods for detecting hepatitis B surface antigens did not satisfy the enablement requirement, and held that the "specification was enabling with respect to the claims at issue and found that 'there was considerable direction and guidance' in the specification; there was 'a high level of

skill in the art at the time the application was filed;' and 'all of the methods needed to practice the invention were well known.'" MPEP §2164.01(a) quoting In re Wands, 858 F.2d at 740, 8 USPQ2d at 1406.

In response, Applicants respectfully traverse the Examiner's above grounds of rejections. Applicants maintain that "an antineoplastic agent which is a microtubule-stabilizing agent" satisfy the requirements of 35 U.S.C. §112, first paragraph. Applicants contend that the specification as originally file would have enabled any person skilled in the pharmaceutical art to practice the claimed invention. Applicants further contend that the specification as filed clearly disclosed the method for treating cancer by administering a pharmaceutical combination of an antineoplastic agent and a prenyl-protein inhibitor simultaneously to inhibit protein prenylation, interfere with DNA replication and/or interfere with cell replication by arresting division of microtubule and/or induce apoptosis.

The Examiner stated that:

> "The claims are drawn to methods and compositions for achieving a synergistic therapeutic effects in mammals in need thereof employing a prenyl-protein transferase inhibitor and an antineoplastic agent which is a microtubule-stabilizing agent."

In response, Applicants contend that the claimed invention as disclosed in the specification as filed provides a method for treating cancer by administering to a mammalian patient an effective amount of a combination of an antineoplastic agent and a prenyl-protein transferase inhibitor. Applicants further contend that the specification, as filed, also disclosed a therapeutic composition and a method for using and making such composition for treating cancer, inhibiting

cancerous tumor growth and/or the regression of cancerous tumors. Applicants further disclosed in the specification that the starting materials, i.e. antineoplastic agents and prenyl-protein transferase which when combined, have a synergistic effect against cancer cells. The specification, as filed, also defined antineoplastic agent as "compounds which either prevent cancer cells from multiplying by interfering with the cell's ability to replicate DNA or induce apoptosis in the cancerous cells." The disclosure would have enabled a person of ordinary skill in the art to treat cancer in a mammalian subject using efficacious combination of the above-mentioned compounds. Furthermore, the disclosure would have enabled a person of ordinary skill to manufacture, produce or derive compositions from said compounds to effectively treat cancer in a mammalian subject without undue experimentation.

The Examiner also stated that:

> "The prior art does not teach the combination [of an antineoplastic agent and prenyl-protein transferase] together will produce synergistic therapeutic effects."

In response, Applicants acknowledge Examiner's above assertions that "prior art does not teach the combination together will produce a synergistic therapeutic effect."

The Examiner also stated that:

> "The level of ordinary skill in the art is high. The genus set forth by the term 'an antineoplastic agent which is a microtubule-stabilizing agent' encompasses a vast number of antineoplastic agent. These agents are employed to form a synergistic therapeutic effect."

In response, applicants respectfully contend that the person of ordinary or ordinary high skill in the pharmaceutical arts would readily expect to perform extensive experiments to identify which combinations of antineoplastic agents that act on microtubules to cause apoptotic cell death and prenyl-protein inhibitors would be clinically efficacious and such person of ordinary or ordinary high skill in the relevant art would determine that such extensive experimentation would not be undue or onerous.

The Examiner also stated that "there is little or no predictability in forming a synergistic therapeutic effect" and that "each combination must be shown."

Applicants respectfully traverse Examiner's above grounds of rejections. In response, Applicants contend that examples set forth in the specification of this Application clearly showed that synergistic activity was observed when a prenyl-protein transferase inhibitor is administered with compounds which belonged to several classes of antineoplastic agents that can stabilize microtubules, such compounds include, but are not limited to paclitaxels and epothilones. Applicants further contend that at the time of the filing of this Application the efficacy of combination therapy of enzyme inhibitors and antineoplastic agents that stabilizes microtubules, have been disclosed. See, Moasser et al. *Proc. Natl. Acad. Sci.*, a copy of which is attached herein as EXHIBIT 1. Moasser et al. was submitted by the Applicants in an Information Disclosure Statement,.

Applicants further contend that the disclosure, considering the level of ordinary or ordinary high skill in the pharmaceutical art as of the date of the Applicants' application, would have enabled a person of such skill to determine, make, use and/or produce pharmaceutically efficacious combinations of antineoplastic agents which

stabilizes microtubules and prenyl-protein transferase for treatment of cancer without undue experimentation. Accordingly, the specifications as filed teach one of ordinary skill in the art that they can anticipate compositions which have therapeutic anticancer effect if they combine prenyl-protein transferase with an antineoplastic agent which are also microtubule stabilizing agents. See Adjei et al., a copy of which is attached herein as EXHIBIT 3, which described an increasing interest in "examining the effects of enzyme inhibitors with other anticancer drugs" or chemotherapeutic agents." (citing Moasser et al.) Therefore, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

The Examiner also stated:

> "The specification on pages 249-300 gives direction in forming a test for the combination. The figures 1-12 and 23-27 give results of the antineoplastic agent which is a microtubule-stabilizing agent and compound A. These limited showings on one compound clearly would not support the large number of synergistic combination set forth in the above claims."

Applicants respectfully traverse the Examiner's above grounds of rejections. Applicants contend that the disclosure, considering the level of ordinary or ordinary high skill in the pharmaceutical art as of the date of the Applicants' application, would have enabled a person of such skill to determine, produce, make and/or use the pharmaceutically efficacious combinations of antineoplastic agents that stabilizes microtubules and prenyl-protein transferase for treatment of cancer without undue experimentation. Applicants further contend that the amount of experimentation to determine the efficacious anticancer agents from both

microtubule stabilizing agents and prenyl-protein inhibitor would not be undue.

Applicants further contend that the disclosure and teachings set forth in the specification of the instant Application, a part of which was published in Moasser et al., has provided motivation to other workers with ordinary or ordinary high skill in the pharmaceutical art to employ enzyme inhibitors with antinoeplastic/microtubule-stabilizing agents to achieve the expected combination and/or synergistic effects. See Pervin et al. (2001) pp. 4701, a copy of which attached herein as EXHIBIT 2. Pervin et al. described combining "Farnesyltransferase inhibitors (FTIs) with a variety of commonly used anticancer agents." Pervin et al further described that "antimicrotubule agents that prevent tubulin depolymerization such as taxanes and vincristine have been shown to synergize with FTIs to affect cancer cell lines" (citing Moasser et al.) Also, See Adjei et al., a copy of which is attached herein as EXHIBIT 3, which described an increasing interest in "examining the effects of enzyme inhibitors with other anticancer drugs" or chemotherapeutic agents." (citing Moasser et al.) Also, See Sun et al. (1999) pp. 4919, which described the "combination therapy of FTI with either cispaltin, gemcitabine, or taxol resulted in greater antitumor efficacy than monotherapy." Sun, J. et al. further described that the "combination therapy of GGTI with cispaltin, gemcitabine or taxol is also more effective." A copy of Sun, J. et al. is attached herein as EXHIBIT 4. Therefore, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

The Examiner also stated that "the term 'an antineoplastic agent which is a microtubule-stabilizing agent' encompasses a vast number of compounds.'" The Examiner further stated that Applicants' "limited number of working examples will not

support such a broad term, moreover, being able to produce a synergistic effect."

Manual for Patent Examining Procedure (MPEP) §2164.02 provides in relevant part:

> "Compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic.' An applicant need not have actually reduced the invention to practice prior to filing." (citing Gould v. Quigg, 822 F.2d 1074, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).
>
> Moreover "the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art would be able to practice it without undue experimentation." (citing In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

In In re Strahilevitz, the examiner rejected the applicant's patent application for methods and devices for removing hapten, antigen or antibody from the blood of a living mammal under 35 U.S.C. §112, first paragraph, citing lack of specific examples. The court held that the applicant's specifications set forth details of routine and well known methods and techniques for selecting and preparing hapten, antigens, and antibodies and that applicant's disclosure would have enabled a person of ordinary skill in the in art to make and use applicant's invention without undue experimentation. In re Strahilevitz, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A. 1982).

Applicants respectfully traverse the Examiner's above grounds of rejections. Applicants maintain that while examples are not required to satisfy the enablement requirement of 35

U.S.C. §112, the examples provided by the Applicants in the specification would enabled one of ordinary skill in the art to select an antineoplastic agent that act on microtubules and a prenyl-protein inhibitor without undue experimentation. Moreover, as state above, the specification has taught a person of ordinary skill, to combine antineoplastic agent with prenyl-protein inhibitor to make pharmaceutical compositions which are efficacious for treating cancer in a mammalian subject. (See Pervin, S. et al., Adjei, A. et al. and Sun, J. et al.) Therefore, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection.

The Examiner stated that the "claims are extremely broad due to the vast number of possible combination that would produce a synergistic therapeutic effect."

Applicants respectfully traverse the Examiner's above ground of rejection. In response, Applicants maintain that the claims are not extremely broad as a person of ordinary skill in the art would be able to use or to make therapeutic anticancer compositions from the class of compounds encompassed by the term antineoplastic agent that are also microtubule-stabilizing agents and enzyme inhibitor, and that when said compounds are combined with enzyme inhibitors, such as prenyl-protein transferase inhibitor, the combination thereof would produce synergistic effect against cancer and/or tumor cells. (See Pervin, S. et al., Adjei, A. et al. and Sun, J. et al.) Therefore, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection

The Examiner stated that:

> "The specification did not enable any person skilled in the art to which it pertains to make or use the invention commensurate in scope with this claim. In particular, the specification failed to enable he

skilled artisan to practice the invention without undue experimentation. The skilled artisan would have a numerous amount of modifications to perform in order to obtain compounds as claimed."

Applicants respectfully traverse the Examiner's above ground of rejection. In response, and also based on the reasons set forth previous in this section, Applicants respectfully contend that the specification as originally filed would have enabled any person with ordinary or ordinary high skill in the art to determine which combinations of antineoplastic agent/microtubule-stabilizing agents and prenyl-protein transferase inhibitors would produce efficacious effect against cancer without performing undue experimentation. Therefore, Applicants respectfully request the reconsideration and withdrawal of this ground of rejection

## Summary

Applicants respectfully contend that the Examiner's objections and/or rejections raised in the July 28, 2003 Final Office Action have been fully addressed, and therefore this Application is in full compliance with all requirements. Accordingly, Applicants respectfully urge the Examiner to reconsider and withdraw all objections and/or rejections in the July 28, 2003 Final Office Action and place this application in conditions for allowance.

Alternatively, if this Proposed Amendment in Response to the July 28, 2003 Final Office Action does not place this Application in condition for allowance, then the Applicants respectfully request the Examiner and/or the Office to treat this Amendment/Communication as a Request for Continued Examination (RCE) with extension of time if necessary, and authorize the Commissioner to charge the appropriate fees to Deposit Account No. 50-1891.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants undersigned Attorney invites the Examiner to telephone him at the number provided below.

No fee other than the TWO HUNDRED AND TEN DOLLARS ($210.00) for the petition for two-month extension of time is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

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I hereby certify that this paper is being deposited this date with the U.S. Postal Service with sufficient postage for first class mail addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Albert Wai-Kit Chan 2/29/03
Albert Wai-Kit Chan Date
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